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USE OF CERTAIN DRUGS FOR TREATING NERVE ROOT INJURY

DESCRIPTION

Technical field

The present invention relates to the use of a TNF-α inhibitor in the preparation of pharmaceutical compositions for the treatment of nerve root injury, as well as a method for treating nerve root injury.

The object of the present invention is to obtain a possibility to treat nerve root injury, which may turn up as sciatica, by blocking disk related cytokines.

Background of the invention

Disk herniation is a troublesome disorder, which causes great pain and lost of motility, and thereby lost of productive life. Disk herniation will cause trouble to a varying degree, and the pain may last for a month or in severe cases up to 6 months. Beside the pain sciatica may cause severe handicapping problems, as the one suffering therefrom will feel crippled thereof.

US-A-5,703,092 discloses the use of hydroxamic acid compounds and carbocyclic acids as metalloproteinase and TNF inhibitors, and in particular in treatment of arthritis and other related inflammatory diseases. No use of these compounds for the treatment of nerve root injuries is disclosed or hinted at.

US-A-4,925,833 discloses the use of tetracyclines to enhance bone protein synthesis, and treatment of osteoporosis.

US-A-4,666,897 discloses inhibition of mammalian collagenolytic enzymes by tetracyclines. The collagenolytic activity is manifested by excessive bone resorption, periodontal disease, rheumatoid arthritis, ulceration of cornea, or resorption of skin or other connective tissue collagen.

Neither of these latter two documents mentions nerve root injury or the treatment thereof.

It has been noted that cytokines from nucleus pulposus-cells such as TNF-α, interleukin 1-β and interferon-γ and others cause structural and functional damages on closely situated nerves in connection with e.g., a disk herniation. Furthermore the nerve becomes sensitised by these substances to produce pain when they are mechanically deformed.

Description of the present invention

It has now surprisingly been shown possible to be able to treat nerve root injuries, or at least alleviate the symptoms of nerve root injuries by using a pharmaceutical composition comprising an therapeutically active amount of a metalloproteinase inhibitor, tetracyclines including chemically modified tetracyclines, quinolones, corticosteroids, cyclosporine, thalidomide, lazaroides, pentoxyphylline, hydroxamic acid derivatives, napthopyrans, soluble cytokine receptors, amrinone, pimobendan, vesnarinone, phosphodiesterase III inhibitors, and melatonin in the form of bases or addition salts together with a pharmaceutically acceptable carrier.

The therapeutically effective amount is a dosage normally used when using such compounds for other therapeutic uses. Many of these drugs are commercially known registered drugs.

Compounds that possess this activity are tetracyclines, such as tetracycline, doxycycline, lymecycline, oxytetracycline, minocycline, and chemically modified tetracyclines dedimethylaminotetracycline, hydroxamic acid compounds, carbocyclic acids and derivatives, cyclosporine, methylprednisolone, thalidomide, lazaroides, pentoxyphylline, napthopyrans, soluble cytokine receptors, amrinone, pimobendan, vesnarinone, phosphodiesterase III inhibitors, melatonin, norfloxacine, ofloxacine, ciprofloxacine, gatifloxacine, pefloxacine, lomefloxacine, and temafloxacine. These can be present as bases or in the form of addition salts, whichever possesses the best pharmaceutical effect, and best property to be brought into a pharmaceutical suitable composition.

Further, the active component comprises a substance inhibiting a compound trigged by the release of TNF-α, such as interferon-gamma, interleukin-1, and nitrogen oxide (NO) in the form of base or addition salts.

The invention further relates to a method for inhibiting the symptoms of nerve root injury.

The effect of doxycycline has been studied and the methods used and results obtained are disclosed below.

Example

Study design.

The effects of nucleus pulposus and various treatments to block TNF-α activity were evaluated in an experimental set-up using immunohistochemistry and nerve conduction velocity recordings.

Summary of background data:

A meta-analysis of observed effects induced by nucleus pulposus reveals that these effects might relate to one specific cytokine, Tumor Necrosis Factor alpha (TNF(α).

Objectives.

To assess the presence of TNF(α) in pig nucleus pulposus cells and to see if block of TNF(α) also blocks the nucleus pulposus-induced reduction of nerve root conduction velocity.

Methods

Series-1: Cultured nucleus pulposus-cells were immunohistologically stained with a monoclonal antibody for TNF(α).

Series-2: Nucleus pulposus was harvested from lumbar discs and applied to the sacro-coccygeal cauda equina in 13 pigs autologously. Four pigs received 100 mg of doxycycline intravenously, 5 pigs had a blocking monoclonal antibody to TNF-α applied locally in the nucleus pulposus, and 4 pigs remained non-treated and formed control. Three days after the application the nerve root conduction velocity was determined over the application zone by local electrical stimulation.

Results.

Series-1: TNF-α was found to be present in the nucleus pulposus-cells.

Series-2: The selective antibody to TNF-α limited the reduction of nerve conduction velocity, although not statistically significantly to the control series. However, treatment with doxycycline significantly blocked the nucleus pulposus-induced reduction of

conduction velocity.

Conclusion.

For the first time a specific substance, Tumor Necrosis Factor-alpha, has been linked to the nucleus pulposus-induced effects of nerve roots after local application. Although the effects of this substance may be synergistic with other similar substances, the data of the present study may be of significant importance for the continued understanding of nucleus pulposus' biologic activity, and might also be of potential use for future treatment strategies of sciatica.

After previously being considered as just a biologically inactive tissue component compressing the spinal nerve root at disc herniation, the nucleus pulposus has recently been found to be highly active, inducing both structural and functional changes in adjacent nerve roots when applied epidurally (24,37,38,41,42). It has thereby been established that autologous nucleus pulposus may induce axonal changes and a characteristic myelin injury (24,38,41,42), increased vascular permeability (9,44), intra vascular coagulation (24,36), and that membrane-bound structure or substances of the nucleus pulposus-cells are responsible for these effects (24,37). The effects have also been found to be efficiently blocked by methyl-prednisolone and cyclosporin A (2,38). When critically looking at these data, one realizes that there is at least one cytokine that relates to all of these effects, Tumor Necrosis Factor alpha (TNF-α). To assess if TNF-α may be involved in the nucleus pulposusinduced nerve root injury the presence of TNF-α in nucleus pulposus-cells was assessed and was studied if the nucleus pulposus-induced effects could be blocked by doxycycline and also by a selective monoclonal antibody.

MATERIAL AND METHODS

Series-1, Presence of TNF-α in pig nucleus pulposus-cells:

Nucleus pulposus (NP) from a total of 13 lumbar and thoracic discs were obtained from a pig used for other purposes. NP was washed once in Ham's F12 medium (Gibco BRL, Paisley, Scotland) and then centrifuged and suspended in 5 ml of collagenase solution in Ham's F12 medium (0.8 mg/ml, Sigma Chemical Co., St Louis, MO, USA) for 40 minutes, at 37°C in 25 cm^2 tissue culture flasks. The separated NP-cell pellets were suspended in DMEM/F12 1:1 medium (Gibco BRL, Paisley, Scotland) supplemented with 1% L-glutamine 200 mM (Gibco BRL, Paisley, Scotland), 50μg/ml gentamycine sulphate (Gibco BRL, Paisley, Scotland) and 10% foetal calf serum (FCS), (Gibco BRL, Paisley, Scotland).

The cells were cultured at 37°C and 5% CO_2 in air for 3-4 weeks and then cultured directly on tissue culture treated glass slides (Becton Dickinson & Co Labware, Franklin Lakes, NJ, USA). After 5 days on the glass slides, the cells were fixed in situ by acetone for 10 minutes. After blocking irrelevant antigens by application of 3% H_2O_2 (Sigma Chemical Co., St Louis, MO, USA) for 30 minutes and Horse Serum (ImmunoPure ABC, peroxidase mouse IgG staining kit nr.32028, Pierce, Rockford, IL) for 20 minutes, the primary antibody (Anti-pig TNF-α monoclonal purified antibody, Endogen, Cambridge, MA, USA) was applied over night at +40°C, diluted at 1:10, 1:20 and 1:40. For control, BSA (bovine serum albumin, Intergen Co, New York, USA) suspended in PBS (phosphate buffered saline, Merck, Darmstadt, Germany) was applied in the same fashion. The next day the cells were washed with 1% BSA in PBS and the secondary antibody (ImmunoPure ABC, peroxidase mouse IgG staining kit nr.32028, Pierce, Rockford, IL) was applied for 30 minutes. To enhance this reaction, the cells were exposed to Avidin-Biotin complex for additionally 30 minutes (ImmunoPure ABC, peroxidase mouse IgG staining kit nr.32028, Pierce, Rockford, IL). The cells were then exposed to 20 mg of DAB (3,3-diaminobenzidine tetrahydrochloride nr. D-5905, Sigma Chemical Co., St Louis, MO, USA) and 0.033 ml of 3% H_2O_2 in 10 ml of saline for 10 minutes. The cells were washed in PBS, dehydrated in a series of ethanol, mounted and examined by light microscopy by an unbiased observer regarding the presence of a brown colouration indicating presence of TNF-α.

Series-2, Neurophysiologic evaluation:

Thirteen pigs, (body weight 25-30 kg) received an intramuscular injection of 20 mg/kg body weight of Ketalar^R (ketamine 50 mg/ml, Parke-Davis, Morris Plains, New Jersey) and an intravenous injection of 4 mg/kg body weight of Hypnodil^R (methomidate chloride 50 mg/ml, AB Leo, Helsingborg, Sweden) and 0. I mg/kg body weight of Stresnil^R (azaperon 2 mg/ml, Janssen Pharmaceutica, Beerse, Belgium). Anaesthesia was maintained by additional intravenous injections of 2 mg/kg body weight of Hypnodil^R and 0.05 mg/kg body weight of Stresnil^R. The pigs also received an intravenous injection of 0.1 mg/kg of Stesolid Novum^R (Diazepam, Dumex, Helsingborg, Sweden) after surgery.

Nucleus pulposus was harvested from the 5th lumbar disc through a retro peritoneal approach (42). Approximately 40 mg of the nucleus pulposus was applied to the sacrococcygeal cauda equina through a midline incision and laminectomy of the first

coccygeal vertebra. Four pigs did not receive any treatment (no treatment). Four other pigs received an intravenous infusion of 100 mg of doxycycline (Vibramycino, Pfizer Inc., New York, USA) in 100 ml of saline over 1 hour. In 5 pigs, the nucleus pulposus was mixed with 100 gl of a 1,11 mg/ml suspension of the anti-TNF-α antibody used in series 1, before application.

Three days after the application, the pigs were reanaesthetized by an intramuscular injection of 20 mg/kg body weight of Ketalar^R and an intravenous injection of 35 mg/kg body weight of Pentothal^R (Thiopental sodium, Abbott lab, Chicago, IL). The pigs were ventilated on a respirator. Anaesthesia was maintained by an intravenous bolus injection of 100 mg/kg body weight of Chloralose (α)-D(+)-gluco-chloralose, Merck, Darmstadt, Germany) and by a continuous supply of 30 mg/kg/hour of Chloralose. A laminectomy from the 4th sacral to the 3rd coccygeal vertebra was performed. The nerve roots were covered with Spongostane^R (Ferrosan, Demnark). Local tissue temperature was continuously monitored and maintained at 37.5-38.0°C by means of a heating lamp.

The cauda equina was stimulated by two E2 subdermal platinum needle electrodes (Grass Instrument Co., Quincy, MA) which were connected to a Grass SD9 stimulator (Grass Instrument Co., Quincy, MA) and gently placed intermittently on the cauda equina first 10 mm cranial and then 10 mm caudal to the exposed area. To ensure that only impulses from exposed nerve fibers were registered, the nerve root that exited from the spinal canal between the two stimulation sites were cut. An EMG was registered by two subdermal platinum needle electrodes which were placed into the paraspinal muscles in the tail approximately 10 mm apart. This procedure is reproducible and represents a functional measurement of the motor nerve fibers of the cauda equina nerve roots. The EMG was visualized using a Macintosh IIci computer provided with Superscope software and MacAdios II AID converter (GW Instruments, Sommerville, MA) together with a Grass P18 preamplifier (Grass Instrument Co., Quincy, MA). The separation distance between the first peaks of the EMG from the two recordings was determined and the separation distance between the two stimulation sites on the cauda equina was measured with calipers. The nerve conduction velocity between the two stimulation sites could thus be calculated from these two measurements.

The person performing the neurophysiologic analyses was unaware of the experimental

protocol for the individual animal, and after finishing the complete study the data were arranged in the three experimental groups and statistical differences between the groups were assessed by Student's t-test. The experimental protocol for this experiment was approved by the local animal research ethics committee.

RESULTS

Series-1, Presence of TNF-α in pig nucleus pulposus-cells:

Examples of the light microscopic appearance of the stained glass slides. In the sections using BSA in PBS as "primary antibody" (control) no staining was observed, ensuring that there was no labelling and visualization of irrelevant antigens. When the anti-TNF-α antibody was applied at 1:40 dilution there was only a weak staining. However, the staining increased with diminishing dilutions of the antibody. The staining was seen in the soma of the cells and it was not possible to differentiate whether TNF-α was located in the cytoplasm, on the cell surface bound to the cell-membrane, or both.

Series-2, Neurophysiologic evaluation:

Application of non-modified nucleus pulposus and without any treatment induced a reduction in nerve conduction velocity similar to previous studies (no treatment, figure 2), whereas treatment with doxycycline completely blocked this reduction ($p<0.01$ Student's t-test). Local application of anti-TNF-α-antibody also induced a partial block of this reduction, although not as complete as doxycycline and not statistically significant to the no treatment-series.

DISCUSSION

The data of the present study demonstrated that TNF-α may be found in nucleus pulposus-cells of the pig. If TNF-α was blocked by a selective monoclonal antibody, the nucleus pulposus-induced reduction of nerve root conduction velocity was partially blocked, although no statistically significant compared to the series with non-treated animals. However, if doxycycline was used to inhibit TNF-α, the reduction of nerve conduction velocity was significantly blocked.

In recent years, it has been verified that local application of autologous nucleus pulposus may injure the adjacent nerve roots. Thus, it has become evident that the nerve root injury seen at disc herniation may not be solely based on mechanical deformation of the nerve root, but may also be induced by unknown "biochemical effects" related to the epidural presence of herniated nucleus pulposus. Although this new research field has generated many

experimental studies, the mechanisms and substances involved are not fully known. It has been seen that local application of autologous nucleus pulposus may induce axonal injury (24,37,38,40-42), a characteristic injury of the myelin sheath (24,38,40-42), a local increase of vascular permeability (9,36,44), intra vascular coagulations, reduction of intra neural blood flow (43), and leukotaxis (36). It has been seen that the nucleus pulposus-related effects may be blocked efficiently by methylprednisolone (38) and cyclosporin A (2), and slightly less efficiently by indomethacin (3), and lidocaine (69). Further, it has been understood that the effects are mediated by the nucleus pulposus-cells (37), particularly by substances or structures bound to the cell-membranes (25). When critically considering these data, it becomes evident that at least one specific cytokine could be related to these observed effects, Tumor Necrosis Factor-alpha (TNF-α). TNF-α may induce nerve injury (29,31,45,50,66) mainly seen as a characteristic myelin injury that closely resembles the nucleus pulposus-induced myelin-injury (29,47,51,54,62,64,66,70). TNF-α may also induce an increase in vascular permeability (47,66) and initiate coagulation (22,34,63). Further, TNF-α may be blocked by steroids (4,8,21,61,68), and cyclosporin A (11,55,67,68). However, the blocking effect on TNF-α is not so pronounced by NSAID (14,17,20) and very low or the opposite by lidocaine (5,32,46,60). It was recently observed that local application of nucleus pulposus may induce pain-related behaviour in rats, particularly thermal hyperalgesia (23,40). TNF-α has also been found to be related to such pain-behaviouristic changes (12,35,56,66), and also to neuropathies in general (30,54,56,57). However there are no studies that have assessed the possible presence of TNF-α in the cells of the nucleus pulposus.

To assess if TNF-α could be related to the observed nucleus pulposus induced reduction in nerve root conduction velocity it was necessary first to analyse if there were TNF-α in the nucleus pulposus-cells. The data clearly demonstrated that TNF-α was present in these cells. TNF-α is produced as precursor (pro-TNF) that is bound to the membrane and it is activated by cleavage from the cell-membrane by a zinc-dependent metallo-endopeptidase (TNF-alpha converting enzyme, TACE) (6,15,16,48,49). This may thus relate well to experimental findings where application of the mere cell-membranes of autologous nucleus pulposus-cells induced nerve conduction velocity reduction, which indicated that the effects were mediated by a membrane-bound substances. Second, the effects of the TNF-α had to be blocked in a controlled manner. We then first choose to add the same selective antibody that was used

for immunohistochemistry in series 1, which is known to also block the effects of TNF-α, to the nucleus pulposus before application. Also, we choose to treat the pigs with doxycycline, which is known to block TNF-α (26,27,33,52,53). However, due to the low pH of the doxycycline preparation it was chosen to treat the pigs by intravenous injection instead of local addition to the nucleus pulposus since nucleus pulposus at a low pH has been found to potentiate the effects of the nucleus pulposus (38,39).

The data regarding nerve conduction velocity showed that the reduction was completely blocked by the doxycycline-treatment and that the nerve conduction velocity in this series was close to the conduction velocity after application of a control substance (retro peritoneal fat) from a previous study (42). Application of the anti-TNF-α-antibody to the nucleus pulposus also partially blocked the reduction in velocity, however, not as pronounced as doxycycline, and the velocity in this series was not statistically different to the velocity in the series with not treated animals, due to the wide deviation of the data.

The fact that the anti-TNF-α antibody treatment only partially blocked the nucleus pulposus-induced reduction of nerve conduction velocity and the high standard deviation of the data could probably have at least two different explanations. First, if looking at the specific data within this group it was found that the nerve conduction velocity was low in 2 animals (mean 37.5 m/s) and high in 3 animals (mean 81.3 m/s). There are thus 2 groups of distinctly different data within the anti-TNF-α treatment series. This will account for the high standard deviation and might imply that the blocking effect was sufficient in 3 animals and non-sufficient in 2 animals. The lack of effects in these animals could be based simply on the amount of antibodies in relation to TNF-α molecules not being sufficient, and if a higher dose of the antibody had been used, the TNF-α effects would thus have been blocked even in these animals. Such a scenario could then theoretically imply that TNF-α alone is responsible for the observed nucleus pulposus-induced effects, and that this could not be verified experimentally due to the amount of antibody being too low.

Second, it is also known that tetracyclines such as doxycycline and minocycline may block a number of cytokines and other substances. For instance they may block IL-1 (1,28,58), IFNγ (27), NO-synthetasel, and metalloproteinases (1,53,58). Particularly IL-1 and IFNγ are known to act synergistically with TNF-α and are known to be more or less neurotoxic

(7,10,13,18,19,56,59). These substances are also blocked by steroids and cyclosporin A which corresponds well with the previous observations on nucleus pulposus-induced nerve root injury which have shown that the nucleus pulposus-induced effects may be blocked by these substances (8,67). One may therefore also consider the possibility that a selective block of TNF-α may not be sufficient to completely block the nucleus pulposus-induced effects on nerve function, and that simultaneous block of other synergistic substances is necessary as well. Thus, this scenario, on the other hand, implies that TNF-α is not solely responsible for the nucleus pulposus-induced effects, and that other synergistic substances, which are also blocked by doxycycline, may be necessary.

TNF-α may have various pathophysiologic effects. It may have direct effects on tissues such as nerve tissue and blood vessels, it may trigger other cells to produce other pathogenic substances and it may trigger release of more TNF-α both by inflammatory cells and also by Schwann-cells locally in the nerve tissue (65).]here is thus reason to believe that even low amounts of TNF-α may be sufficient to initiate these processes and that there is a local recruitment of cytokine producing cells and a subsequent increase in production and release of other cytokines as well as TNF-α. TNF-α may therefore act as the "ignition key" of the pathophysiologic processes and play an important role for the initiation of the pathophysiologic cascade behind the nucleus pulposus-induced nerve injury.

In conclusion, although the exact role of TNF-α can not be fully understood from the experimental set-up, we may conclude that for the first time a specific substance (TNF-α) has been linked to the nucleus pulposus-induced nerve root injury, probably potentiated by other substances which are also blocked by doxycycline, such as for instance IL1, IFNγ and NO-synthetase. This new information may be of significant importance for the continued understanding of nucleus pulposus-induced nerve injury as well as raising the question of the potential future clinical use of pharmacological interference with TNF-α and related substances, by for instance doxycycline or metalloproteinase-inhibitors, for the treatment of sciatica.

The presence of TNF-α in pig nucleus pulposus-cells was thus immunohistochemically verified. Block of TNF-α by a monoclonal antibody partially limited the nucleus pulposus-induced reduction of nerve root conduction velocity, whereas intravenous treatment with

doxycycline significantly blocked this reduction. These data for the first time links one specific substance, TNF-α, to the nucleus pulposus-induced nerve injury.

Aminoguanidine has showed to inhibit the release of nitrogen oxide (NO) at nerve root injuries by inhibiting inducible nitrogen oxide synthetase, and aminoguanidine is thus one compound that inhibits a compound trigged by the release of TNF-α.

The compounds of the invention can be administered in a variety of dosage forms, e.g, orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions; rectally, in the form of suppositories; parenterally, e.g., intramuscularly or by intravenous injection or infusion. The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology taken in to account, as usual, also the route of administration, the form in which the compound is administered and age, weight, and condition of the subject involved.

The oral route is employed, in general, for all conditions, requiring such compounds. In emergency cases preference is given to intravenous injection. For these purposes the compounds of the invention can be administered orally at doses ranging from about 20 to about 1500 mg/day. Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

The nature of the pharmaceutical composition containing the compounds of the invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired route of administration. The composition may be formulated in the conventional manner with the usual ingredients. For example, the compounds of the invention may be administered in the form of aqueous or oily solutions or suspensions, tablets, pills, gelatine capsules (hard or soft ones)syrups, drops or suppositories.

Thus for oral administration, the pharmaceutical compositions containing the compounds of the invention are preferably tablets, pills or gelatine capsules, which contain the active substance together with diluents, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, e.g., silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methyl cellulose, carboxymethylcellulose, gum arabic, tragacanth, polyvinylpyrrolidone;

disaggregating agents such as starches, alginic acid, alginates, sodium starch glycolate, microcrystalline cellulose; effervescing agents such a carbonates and acids; dyestoffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and in general non-toxic and pharmaceutically inert substances used in the formulation of pharmaceutical compositions. Said pharmaceutical compositions may be manufactured in known manners, e.g., by means of mixing, granulating, tableting, sugar-coating or film-coating processes. In the case film providing compounds can be selected to provide release in the right place in the intestinal tract with regard to absorption and maximum effect. Thus pH-dependent film formers can be used to allow absorption in the intestines as such, whereby different phthalate are normally used or acrylic acid/methacrylic acid derivatives and polymers.

The liquid dispersions for oral administration may be e.g., syrups, emulsion, and suspensions.

The syrups may contain as carrier, e.g., saccharose, or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, e.g., a natural gum, such as gum arabic, xanthan gum, agar, sodium alginate, pectin, methyl cellulose, carboxymethylcellulose, polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain together with the active compound, a pharmaceutically acceptable carrier, such as e.g., sterile water, olive oil, ethyl oleate, glycols,, e.g., propylene glycol, and if so desired, a suitable amount of lidocaine hydrochloride. Adjuvants for trigging the injection effect can be added as well.

The solutions for intravenous injection or infusion may contain as carrier, e.g., sterile water, or preferably, a sterile isotonic saline solution, as well as adjuvants used in the field of injection of active compounds.

The suppositories may contain together with the active compound, a pharmaceutically acceptable carrier, e.g., cocoa-butter polyethylene glycol, a polyethylene sorbitan fatty acid ester surfactant or lecithin.

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CLAIMS

1. Pharmaceutical composition for the inhibition of spinal disk TNF-α for the treatment of nerve root injury comprising a pharmaceutically effective amount of TNF-α inhibiting compound selected from metallo proteinase inhibitors, tetracyclines including chemically modified tetracyclines, quinolones, corticosteroids, cyclosporine, thalidomide, lazaroides, pentoxyphylline, hydroxamic acid derivatives, carbocyclic acid, napthopyrans, soluble cytokine receptors, amrinone, pimobendan, vesnarinone, phosphodiesterase III inhibitors, and melatonin in the form of bases or addition salts together with a pharmaceutically acceptable carrier.

2. Pharmaceutical composition according to claim 1, wherein the active component is selected from the group consisting of tetracycline, doxycycline, lymecycline, oxytetracycline, minocycline, and chemically modified tetracyclines dedimethylaminotetracycline, in the form of bases or addition salts.

3. Pharmaceutical composition according to claim 2, wherein the active component is doxycycline.

4. Pharmaceutical composition according to claim 1, wherein the active component is selected from hydroxamic acid compounds, carbocyclic acids and derivatives, cyclosporine, methylprednisolone, thalidomide, lazaroides, pentoxyphylline, napthopyrans, soluble cytokine receptors, amrinone, pimobendan, vesnarinone, phosphodiesterase III inhibitors, melatonin in the form of bases or addition salts.

5. Pharmaceutical composition according to claim 1, wherein the active component is selected from norfloxacine, ofloxacine, ciprofloxacine, gatifloxacine, pefloxacine, lomefloxacine, and temafloxacine in the form of bases or addition salts.

6. Pharmaceutical composition according to claim 1, wherein the corticosteroid is methylprednisolone in the form of base or addition salts.

7. Pharmaceutical composition according to claim 1, wherein the active component is a metallo proteinase inhibitor in the form of base or addition salts.

8. Pharmaceutical composition according to claim 1, wherein the active component comprises a substance inhibiting a compound trigged by the release of TNF-α, such as interferon-gamma, interleukin-1, and nitrogen oxide (NO) in the form of base or addition salts

9. Method for the treatment of spinal disorders as nerve root injury caused by the liberation of TNF-α in mammals, including man, comprising the administration of a pharmaceutically effective amount of a metallo proteinase inhibitor, a tetracycline including chemically modified tetracycline, a quinolone, a corticosteroids, a cyclosporine, thalidomide, lazaroides, pentoxyphylline, a hydroxamic acid derivative, carbocyclic acid, a napthopyran, a soluble cytokine receptor, amrinone, pimobendan, vesnarinone, a phosphodiesterase III inhibitor, and melatonin in the form of the base or its addition salt.

10. Use of a metallo proteinase inhibitor, a tetracycline including chemically modified tetracycline, a quinolone, a corticosteroids, a cyclosporine, thalidomide, lazaroides, pentoxyphylline, a hydroxamic acid derivative, a carbocyclic acid, a napthopyran, a soluble cytokine receptor, amrinone, pimobendan, vesnarinone, a phosphodiesterase III inhibitor, and melatonin in the form of the base or its addition salt, in the preparation of a pharmaceutical composition for the treatment of spinal disorders as nerve root injury caused by the liberation of TNF-α and compounds trigged by the liberation of or presence of TNF-α.

ABSTRACT

The present invention relates to pharmaceutical compositions for the treatment of spinal disorders caused by the liberation of TNF-α comprising an effective amount of a metallo-proteinase inhibitor, as well as method for treatment of such disorders, and the use of metallo- proteinase inhibitors in the preparation of pharmaceutical composition for such treatment.